First Rejection Under 35 U.S.C. § 112, First Paragraph

1. Status

In the Office Action dated June 5, 2000, claims 62-83 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. While the Examiner acknowledges that the specification is enabling for cells, methods of delivery, and treatment involving a liposome containing a catalytic nucleic acid *in vitro*, it is alleged that the specification is not enabling for delivery to any whole organism. In maintaining the rejection, the Examiner states that "one of skill in the art would not accept on its face the successful delivery, and further treatment effects of the claimed catalyst compositions in whole organisms other than mice..." (*see,* page 3, lines 12-14 of the Office Action mailed June 5, 2000). More particularly, the Examiner alleges that undue experimentation would be required to practice the invention in any whole organism.

*2. Undue experimentation is **not** required*

A particular claim is enabled by the disclosure in an application if the disclosure, at the time of filing, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention ***without*** undue experimentation. *See, e.g., In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988), or MPEP §2164.01. It is important to note that the possibility that some experimentation, even if such experimentation is complex or extensive, may be required for the practice of the invention does not necessarily mean that the invention is not enabled:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See*, MPEP § 2164.01.

Applicants respectfully submit that, in view of the state of the art, the use of the presently claimed liposomal ribozyme compositions in any whole organism is entirely routine. The Examiner has provided no evidence that undue experimentation would be required to practice the invention in organisms other than mice, such as humans. The specification provides substantial teaching regarding how to make the

claimed liposomal ribozyme formulations and how to administer the liposomal ribozyme formulations to a mammal, including humans, having neoplasia. For example, suitable pharmaceutical compositions are taught in the specification, *e.g.*, on page 28, lines 2-13, and on page 28, line 29, to page 29, line 23. In addition, systemic administration of the compositions is taught in the specification, *e.g.*, on page 28, lines 14-28, and methods of determining a pharmaceutically effective dose are taught in the specification, *e.g.*, on page 29, lines 23-31. Finally, several Examples are provided in the specification that teach the administration of the formulation to mammals and that unequivocally demonstrate the stability, tumor cell targeting, and ability of the formulations to inhibit the growth of tumors *in vivo*. *See, e.g.*, Examples 3-6, found in the specification at page 30, line 25 to page 35, line 29.

Apparently, the primary basis for the Examiner's assertion of undue experimentation is the fact that the specification does not provide data showing that the liposomal compositions function effectively in whole organisms other than mice. This basis for rejection is clearly improper in light of the statements in the attached declaration of Dr. Sandra K. Klimuk, an inventor of the present application. Dr. Klimuk's declaration attests to the universality of the belief among scientists that work in experimental animals, such as mice, is of critical importance and relevance to other animals, including humans.

Furthermore, as noted in the response to the previous Office Action, the position among scientists regarding the importance of mouse models is reflected in the case law. For example, in *In re Jolles*, 206 USPQ 885 (CCPA 1980), the CCPA stated that:

> This court recognizes 'that a demonstration that a compound has desirable or beneficial properties in the prevention, alleviation, or cure of some disease or manifestation of a disease in experimental animals does not necessarily mean that the compound will have the same properties when used with humans.' However, this is by no

> means support for the board's position that such evidence is not relevant to human utility.
>
> ***To the contrary, this court has accepted tests on experimental animals as sufficient to establish utility****....*
> *Id.* at 890 (citations omitted; emphasis added).

Therefore, in view of the attached declaration and *In re Jolles*, data in mice is more than sufficient to enable the invention in other organisms, including humans.

Dr. Klimuk's declaration also describes additional mouse studies demonstrating the ability of anti-VEGFR ribozymes to inhibit tumor growth and metastasis, thus providing further support for the conclusion that the ribozyme compositions of the present invention would also function effectively in other mammals, including humans.

In view of the foregoing remarks and Dr. Klimuk's declaration, the Examiner cannot properly assert that undue experimentation would be required to practice the claimed invention. As such, the rejection is improper and should be withdrawn.

Second Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner also alleges that there is a lack of guidance for successful therapeutic administration of ribozymes other than the anti-VEGFR ribozyme. Applicants respectfully submit that the Examiner has provided no reason why one of skill in the art would expect the pharmacokinetic behavior of liposomes containing other ribozymes to differ significantly from those containing the anti-VEGF ribozyme. The increased stability and cellular targeting *in vivo* of the liposomal compositions of the present invention are a consequence of the liposome encapsulating the ribozyme, rather than the catalytic properties of the encapsulated ribozyme. Therefore, the liposomal compositions of this invention containing any nucleic acid catalyst should be delivered to neoplastic cells *in vivo* to approximately the same degree as the liposome-encapsulated anti-VEGFR ribozyme. In order to make a proper enablement rejection, the Examiner

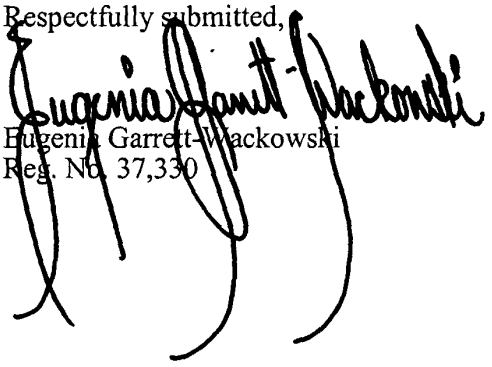
has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. (*In re Wright* 27 USPQ2d 1510 (Fed. Cir. 1993)). In the absence of such showing, the rejection is improper and should be withdrawn. Accordingly, Applicants urge the Examiner to withdraw the rejection under 35 U.S.C. 112, first paragraph.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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